UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/587,150 | 07/24/2006 | Peter Herold | 2006_0980A | 4977 |

513 7590 08/31/2009

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

| EXAMINER | |
|---|---|
| MABRY, JOHN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/31/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/587,150 | HEROLD ET AL. | |
| | Examiner | Art Unit | |
| | JOHN MABRY | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-7,12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***Response to Applicant's Remarks***

Applicant's response on April 27, 2009 filed in response to the Office Action dated December 26, 2008 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

***Status of the Claims***

Claims 1, 4, 5, 6, 7, 12 and 14-18 are pending and rejected.

Claims 15-18 are new.

Claims 2, 3, 5, 8-11 and 13 have been cancelled.

***35 USC § 112 Rejection(s)***

The 112-2nd rejection regarding the term "carbocyclic" has been overcome in view of Applicants amending the claims.

The 112-1st rejection regarding the terms "use of a compound" has been overcome in view of Applicant cancelling the claims.

The 112-1st rejection of claims 1, 4, 7 and 12 regarding the scope of enablement for the entire scope as claimed for R1, R2, R3, R4, R5 and R and claimed substituents have not been overcome in view of Applicants amending the claims. In previously described Non-Final Office Action, Examiner clearly outlined the compounds Applicant

was enabled and the compounds which Applicant is not enabled for regarding claimed compounds of Formula I.

For instance, Applicant claims R1 and a combination of R1 and R2 to heterocyclyl. The definition of heterocyclyl is defined below as shown below (see bottom of page 3 and top of page 4 of the Specification). Applicant is not enabled for scope of instant invention as claimed.

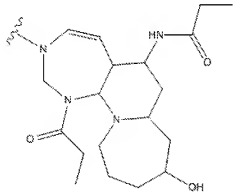
> Heterocyclyl bonded via a ring carbon or ring nitrogen atom contains generally from 4 to 8, in particular from 5 to 7, ring atoms, and may have 1 or 2 fused-on phenyl or cycloalkyl radicals, or else be present as a spiro compound. Examples include pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, tetrahydrofuranyl, furanyl, pyranyl, tetrahydropyranyl, thiazolyl, oxazolyl, imidazolyl, indolinyl, isoindolinyl, 2,3-dihydrobenzimidazolyl, 1,2,3,4-
>
> tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydro-1,3-benzodiazinyl, 1,2,3,4-tetrahydro-1,4-benzodiazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 3,4-dihydro-2H-1,3-benzothiazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzoxazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzothiazinyl, 2,3,4,5-tetrahydro-1H-1-benz[6,7-b]azepinyl and 5,6-dihydrophenanthridinyl. The radicals mentioned may be unsubstituted or N-substituted and/or C-substituted, in which case in particular 1, 2 or 3 substituents may be present.

Applicant argues that given the starting materials and guidance as disclosed in the Specification, one of ordinary skill in the art would be able to prepare the claimed compounds with undue experimentation. Examiner respectfully disagrees.

As disclosed in Specification, there is support for R1 and R2 being H, tetrahydropyranylalkylcarbonyl, piperidinyl alkylcarbonyl, alkylcarbonyl, phenyloxyalkylcarbonyl, acetyl, phenylalkanoyl, cyclohexylalkylsulfonyl, alkyl,

cyclohexylcarbonyl, alkylaminoalkyl, imidazoylalkylphenyl, alkylaminecarbonyl, indenealkylcarbonyl, pyridinylalkylcarbonyl.

For instance, according to the instantly claimed invention, Applicant claims R1 and R2 in combination with the N atom to which they are bonded claims the following structure.




Clearly, based upon the starting material and guidance as provided by the Specification, Applicant is not enabled for the claimed scope. One of ordinary skill in the art would not have sufficient guidance to make the compounds of the claimed scope (i.e. in absence of starting materials or how to make starting material and synthetic guidance on how to make claimed compounds of Formula I). A skilled artisan would clearly be burden with undue experimentation in order to carry out the instant claimed invention.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has not provided sufficient guidance for the artisan to make the invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the

evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The 112-1st rejection of claims 6 and 14-18 regarding the enablement requirement have not been overcome in view of Applicant's remarks. In previously described Non-Final Office Action, Examiner clearly outlined the compounds Applicant was enabled for the claimed methods.

Applicant argues that the enablement rejection should be withdrawn due to information of pages 17 and 18 of Specification –

> "The compounds of the present invention exhibit inhibiting actions in the in vitro systems at minimum concentrations of about $10^{-6}$ to about $10^{-16}$ mol/l."

Just because Applicant's "undisclosed" compounds exhibit *in vitro* IC50 values, does not enable the claimed compounds for treatment or prevention of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis.

**Note:** Applicant has cited Nussberger et al J. Cardiovascular Pharmacol. 1987, 9, 39-44 has not provided reference, but relies on it's guidance as a key feature regarding enablement of the instant invention. Examiner attempted to retrieve said reference, but was only successful at retrieving only the abstract. Did Applicant follow exact experimental of cited reference? Were only certain aspects used from cited reference?

Were double blind studies executed by Applicant using claimed invention using the guidance in cited reference?

Examiner clearly described how lack of *in vitro* or *in vivo* test data may be not sufficient to show treatment and/or prevention of claimed diseases. The following is used to as further support to rebut Applicant's arguments.

The state of the prior art is not well developed and is highly unpredictable. According to the Specification, Applicant's compounds (as listed above) are alleged to treatment or prevention of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis. However, the Specification does not set forth any guidance for *in vitro* assays – only vaguely providing a range of IC50 values of undisclosed compounds. There are no teachings of how to use the claimed compounds *in vivo*. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant Specification would treat related diseases and disorder and altering related physiological functions and disorders in a mammal more specifically treatment or prevention of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis using claimed compounds *in vitro* or *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that election species would treat or prevent of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis. with undisclosed species of Formula I. Applicant has not shown any cell culture data or *in vivo* studies for treating affected mammals. The Applicant has not shown any art recognized correlation between the

data shown and the scope of the claimed invention.

Even in the event the Applicant did provide *in vivo* and *in vitro* studies, the ordinary artisan would recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of in vivo therapy. In the in vitro assay, the agent is in contact with cells during the entire exposure period. This is not the case *in vivo* where exposure to the target site may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological activation. In addition, the composition may not reach the target cells because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat affected patients. One is only left with speculation and an invitation to experiment. Given the breadth of the claims which encompass treatment and the lack of examples and guidance as discussed above, one of ordinary skill in the art would reasonably have considered that at the time the application was filed, that the Applicant was not in possession of the claimed invention.

***Obviousness-Type Double Patenting Rejection(s)***

The obviousness-type double patenting rejected has not been overcome over US copending Application No. 2007/0021399 (11/488,858). A properly executed Terminal Disclaimer is required to overcome rejection.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625